CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
PHOSPHINE

Chemical Code #3541, **Tolerance** # 51882
SB 950 # NA

Original Date 2/26/1
Revised 5/01/02, 9/14/07

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	Data gap, no study on file †
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	Data gap, no study on file †
Reproduction, rat:	Data gap, no study on file †
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	Data gap, no study on file †
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

† Aluminum phosphide and magnesium phosphide both release phosphine upon exposure to water. These two metal phosphides are “grouped” with one another for purposes of registration. The studies evaluated under SB-950 for these two metal phosphides are all found in the Summary of Toxicology Data for aluminum phosphide. None of those studies are acceptable under FIFRA guidelines. Data waivers have been extended for SB-950-mandated studies for these two metal phosphides, and a similar waiver has been requested for phosphine, based on its relationship to the metal phosphides. All of the studies in the present Summary of Toxicology Data involve the exposure of test animals or test systems to phosphine gas. Aldous, 2/26/01.

All record numbers for phosphine (Tolerance No. 51882) through Record #233798 (Document No. 51882-029) were examined. This includes all records indexed by DPR as of 9/14/07.

Revised by Moore, 9/14/07.

In the one-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 51882-006 176429 Newton, P.E., "2-Year combined inhalation chronic toxicity and oncogenicity study of phosphine in rats," MPI Research, Mattawan, MI, 9/10/98. MPI Research Study ID: 750-001. Charles River Fischer [CDF® (F-344)/Crl/BR VAF/Plus®] rats, 50/sex/group, were dosed with phosphine gas by whole body inhalation for 5 days/wk, 6 hr/day at 0, 0.3, 1.0 or 3.0 ppm for 2 years. An additional 10/sex/group were similarly maintained for 1 year for interim sacrifice. There were no treatment effects evident at any dose levels tested (NOEL $\geq$ 3 ppm). Study is acceptable, with no adverse effect. Aldous, 2/26/01.

51882-011 176435 (Identical to 51882-017 186174) Newton, PE., R.J. Hilaski, D.A. Banas, N.H. Wilson, W.M. Busey, and D.G. Shaheen, "A 2-year inhalation study of phosphine in rats" *Inhalation Toxicology* **11**:693-708 (1999). This article summarized information Record No. 1764209 above. No DPR worksheet of this review. Aldous, 4/23/02.

CHRONIC TOXICITY, RAT

See combined, rat: above.

CHRONIC TOXICITY, DOG

No chronic dog studies have been submitted at this time.

ONCOGENICITY, RAT

See combined, rat: above.

ONCOGENICITY, MOUSE

No mouse oncogenicity studies have been submitted at this time.

REPRODUCTION, RAT

No reproduction studies have been submitted at this time.

TERATOLOGY, RAT

**51882-007 176430 Schroeder, R. E., "An inhalation developmental toxicity study of phosphine (PH_3) in rats," Bio/dynamics, Inc., 5 Dec. 1989. Project No. 89-3413. CD® dams, 24/group, were dosed on gestation days 6-15 for 6 hr/day with phosphine by whole-body inhalation at 0, 0.03, 0.3, 3.0, or 5.0 ppm [equivalent to 0, 0.042, 0.42, 4.2 and 7.0 mg/m^3] in a standard teratology study. An additional group was initiated on study at 7.5 ppm [10.5 mg/m^3], however this group was terminated after the first 14 dams at this dose died on or before day 10 of treatment. Aside from the terminated group, there were no treatment effects on body weight, food consumption, clinical signs, or necropsy changes in any groups. Maternal NOEL = 5 ppm (mortalities at 7.5 ppm). Developmental NOEL = 5 ppm (no treatment effects observed). The study is acceptable, with some deficiencies as noted in the review. No adverse effects. Aldous, 2/26/01.

TERATOLOGY, RABBIT

No rabbit teratology studies have been submitted at this time.

GENE MUTATION

**51882-008 176431 Stankowski, Jr., L. F., "Ames/Salmonella plate incorporation assay on hydrogen phosphide (PH_3)," Pharmakon Research International, Inc., 2/10/90. Lab Project ID: PH 301-DA-001-89. Phosphine (from a cylinder containing 1% phosphine in nitrogen) was mixed

with air in a range of concentrations and introduced into dessicators containing plates, prepared in triplicate with six strains of Salmonella typhimurium in the plate incorporation assay. Functional positive controls validated the responsiveness of the strains to known mutagens. There were no consistent patterns of revertants suggestive of a treatment effect over five trials. The study has several deficiencies, including difficulties at providing the desired concentrations of a.i. Gas samples were assayed from each treated dessicator, providing sufficient numbers of plates over an acceptable range for an interpretable study. Acceptable, with no adverse effects. Aldous, 2/15/01.

CHROMOSOME EFFECTS

****51882-009 176432** SanSebastian, J. R., "Structural chromosomal aberration: Chinese hamster ovary (CHO) cell induced by hydrogen phosphide (PH_3)," Pharmakon Research International, Inc., 3/8/90. Lab Project ID: PH 320-DA-001-89. CHO-K1-BH4 cells, Lot #A-12 and A-1, were treated for 5 hr with phosphine ("10,000 ppm in N_2") at 500, 2500, or 5000 ppm (phosphine was metered into serum bottles). After treatment, cells were maintained for an additional 8, 18, or 26 hr (with or without S-9) in fresh medium. Colcemid was added during the last 2-3 hr of post-treatment incubations. Cells were collected after trypsinization, then prepared for reading of 300 metaphase spreads for each dose level, time interval, with or without S-9. Positive controls were MNNG (without S-9, functional) and 1,2-butadiene (with S-9, weakly functional or dysfunctional). Phosphine was weakly positive with and without S-9 at 2500 and 5000 ppm in the 8-hr incubation series only (a possible adverse effect). Study is acceptable, with several deficiencies as noted in the review. Aldous, 2/26/01.

51882-0029; 233798; "Determination of Genotoxic and Other Effects in Mice Following Short Term Repeated-Dose and Subchronic Inhalation Exposure to Phosphine"; (A. Barbosa, E. Rosinova, J. Dempsey and A.M. Bonin; Toxicology Unit, National Institutes of Occupational Health and Safety, Worksafe Australia, Sydney, Australia; Department of Occupational Health, FHDF, Brasilia, Brazil; Department of Human Nutrition, CSIRO, Adelaide, Australia; *Environmental and Molecular Mutagenesis* 24:81-88 (1994)); Twelve Balb-c mice/sex/group were exposed whole-body to 0, 0.3, 1.0 or 4.5 ppm (0, 0.4, 1.4, 6.3 mg/m^3 at STP) of phosphine for 6 hours/day, five days/week for 13 weeks. Upon conclusion of the exposure period, assays for the induction of micronuclei in the polychromatic erythrocytes (PCE) of the bone marrow and in the binucleated lymphocytes (BN) of the spleen were performed. In addition, an assay for the mutation of the HPRT locus in the splenic lymphocytes was undertaken. A preliminary study was performed in which 6 mice/sex were exposed to 5.5 ppm of the test material for 6 hours/day, 5 days/week for 2 weeks. At the conclusion of this period, assays for the induction of micronuclei in kerotinocytes of the skin and in polychromatic erythrocytes of the peripheral blood were performed. The mean body weights gains of both sexes in the exposed groups of the subchronic study were lower than the control values in a dose-related manner. Although some of the relative organ weights of the exposed females were greater than the values for the controls, the biological significance of these effects could not be determined as no microscopic examination of these organs was performed. The females in the 4.5 ppm demonstrated an increased incidence of micronuclei in the PCE of the bone marrow (0: 2.6/1000 PCE vs. 4.5: 5.8/1000 PCE). However, in the authors' evaluation this increase did not constitute a relevant effect. The increased induction of micronuclei in the binucleated lymphocytes of both sexes in the 4.5 ppm exposure group was reported to be significant ((M) 0: 3.3/1000 BN vs. 4.5: 6.3/1000 BN, (F) 0: 3.4/1000 BN vs. 4.5: 7.5/1000 BN) ($p<0.05$). However, no analysis of the splenic lymphocytes from the animals in the intermediate exposure groups was performed. Analysis of the HPRT mutation frequency did not reveal any treatment-related effect. In the shorter-term study, no increase in the induction of micronuclei in the kerotinocytes or in the PCE in the peripheral blood was noted. **Possible adverse effect:** The increased induction of micronuclei in the PCE of the bone marrow of the females and in binucleated lymphocytes of the spleen of both sexes at the highest exposure concentration indicate a potential for genotoxicity in the mouse. **Study supplemental** (not a guideline genotoxicity study). (Moore, 6/28/07)

DNA DAMAGE

**51882-010 176433 McKeon, M. E., "Genotoxicity test on phosphine in the in vivo/in vitro assay for unscheduled DNA synthesis in rat primary hepatocyte cultures at two timepoints," Hazleton Washington, Inc. [in-life phase performed at Pharmaco LSR Inc.], 7/2/93, HWA Study No. A0040-0-494. Male CDF®(F-344)/CrlBR rats, generally 5/dose/time interval, were exposed by inhalation for 6 hr to 0, 5, 13, 18, or 23 ppm phosphine (99.98% purity). Labored breathing was seen at 18 and 23 ppm immediately post-exposure, returning to normal within 2 hr. Body weight losses occurred at 13 to 23 ppm. Sacrifice intervals were about 2 or 12 hr after dosing. Positive controls received dimethylnitrosamine (DMN) ip (10 or 15 mg/kg for 2 and 12-hr post-exposure groups, respectively). Hepatocytes were obtained by collagenase treatment, and were allowed to form monolayers on plastic slides within dishes, each containing about 5×10^5 viable cells. After about 2 hr incubation to establish monolayers, unattached cells were removed and medium was added containing 10 µCi/ml of ^{3}HTdr. After 4 hr, labeled medium was replaced with fresh medium containing 0.25 mM thymidine, and incubation continued for about 18 hr. Slides were removed, dried, and nuclei were swollen. Slides were fixed, dried, dipped in emulsion, which exposed to record radiolabel, and then cells were stained for automatic evaluation. Typically, 3 slides per rat providing 150 readable cells were evaluated for UDS. Results were uniformly negative in the presence of viable positive controls. Study is acceptable, with no adverse effect. Aldous, 2/26/01.

NEUROTOXICITY

Not required at this time (no studies have been submitted).

OTHER STUDIES

**51882-005 176428 Newton, P. E., "A thirteen week inhalation toxicity study of phosphine (PH_3) in the rat," Bio/dynamics, Inc., 3/2/90. Project No. 87-8030. Thirty Fischer 344 rats per sex per group were exposed to phosphine gas, 1.04% average a.i. in nitrogen, by inhalation at 0, 0.3, 1.0, or 3.0 ppm for up to 13 weeks in the core study. Exposures were 6 hr/day, 5 days/wk. Of the 30 rats/sex in each group, 10 were allocated for interim sacrifice after 4 weeks, 10 at the end of 13 weeks, and 10 after 13 weeks of exposure plus 4 weeks of recovery. Due to a meager treatment response in this range, additional groups of 10/sex were dosed with 10 ppm and 5 ppm phosphine, dividing each of these groups between terminal sacrifice and recovery sacrifice subgroups. Groups of 6/sex controls were run in parallel with each of the latter groups. Basic subchronic study parameters were evaluated. This study did not define a NOEL. The most consistent evidence of an organ effect at 3 ppm was in kidneys, where pelvic mineralization was exclusively limited to 3 ppm males, and tubular mineralization was elevated in 3 ppm males (incidence of 10/10, vs. 5/10 in controls). Intermediate dose groups were not evaluated for histopathology. Four of the ten 10 ppm females placed on study died after 3 days of dosing, at which time that treatment level was terminated. Kidneys of all 10 ppm rats examined at death or immediately after the 3-day dosing regimen showed renal tubular necrosis. The study is acceptable, however the report would be improved if appended by histopathology for kidney sections of intermediate dose groups of males (0.3 and 1.0 ppm), in order to avoid use of an "estimated no effect level." No adverse effects are indicated. Aldous, 2/26/01.

51882-004 176427 Newton, P. E., "An acute inhalation toxicity study of phosphine (PH_3) in the rat," Bio/dynamics, Inc., 9/5/89. Project No. 87-8029. Fischer 344 rats, 15/sex/group, were dosed in one 6-hr exposure to phosphine gas. Chamber atmospheres were supplied from a tank containing 1.06% a.i. in nitrogen, at assayed levels of 0, 2.4, 4.9, or 11 ppm. Parameters evaluated included clinical signs, body weights, full necropsies, and limited histopathology (of only the 5/sex/group which were killed on the day of exposure, with only 5 major organs evaluated). There were no definitive effects noted (NOEL = 11 ppm). Study is supplemental (not a required study design), but valid for its intended purposes. No adverse effects are indicated. Aldous, 2/26/01.

51882-011 176436 Schaefer, G. J., P. E. Newton, M. M. Gruebbel, W. M. Busey, and D. G. Shaheen, "Acute and subchronic inhalation neurotoxicity of phosphine in rats," *Inhalation Toxicology* **10**:293-320 (1998). In the **acute** study, CD rats (11/sex/group) were dosed with 0,

21, 28, or 40 ppm phosphine for 4 hr in a single whole-body inhalation exposure. Motor activity and FOB assessments were performed pre-test, and after exposure at 1 hr (peak response time) and at 7 and 14 days. Neurohistopathological evaluations were performed on 6/sex/group after 14 days. The 1-hr motor activity responses included about 50% decrements in horizontal and vertical activity counts in all treated groups (no clear dose-response) compared to controls during at least the first two 10-minute intervals. There were also marked decrements for at least the first 20 minutes in "total distance traveled" per time and in the amount of time spent in stereotypy (defined by investigators as total time spent in repetitive movements). After 20 minutes, all of these measures were reduced in all groups as rats habituated to the motor observation arena, but some treatment effects were still evident. None of these changes were evident after 7 or 14 days of recovery. The acute study did not elicit treatment responses in the FOB at any evaluation period. None of these rats demonstrated neurohistopathologic changes. All of these rats survived, however a single 40 ppm male displayed emaciation and discolored urine as a plausible treatment effect. In the **subchronic** study, 16 rats/sex/group were dosed with 0, 0.3, 1, or 3 ppm phosphine for 13 wk at 6 hr/day, 5 days/wk. Motor activity and FOB assessments were performed pre-test, and after weeks 4, 8, and 13 of treatment. An additional 6 rats/sex/group in 0 and 3 ppm groups were taken off treatment for 2 weeks at termination for recovery evaluation. All of the protocol parameters were negative for the subchronic tests. Thus these acute and subchronic neurotoxicity studies found no noteworthy findings except for a transient pharmacological response after dosing with 20-40 ppm phosphine. No worksheet (insufficient detail for DPR review), no adverse effects indicated. Note: Another copy of this publication was later submitted as 51882-017 186173. Aldous, 2/26/01, edited by Aldous, 4/23/02.

51882-011 176434 Newton, P. E., R. E. Schroeder, J. B. Sullivan, W. M. Busey, and D. A. Banas, "Inhalation toxicity of phosphine in the rat: acute, subchronic, and developmental," *Inhalation Toxicology* **5**:223-239 (1993). This article summarized information Record Nos. 176427, 176428, and 176430, above. No DPR worksheet of this review. Aldous, 2/6/01.

51882-016 186146 Klimmer, O. R., "Contribution to the study of the action of phosphine (PH_3)," reprinted translation of "Beitrag zur Wirkung des Phosphorwasserstoffes (PH_3)" from "Archiv für Toxikologie" 24:164-187 (1969). This article sought to find whether a truly "chronic" response exists to phosphine. Two groups of animals were exposed via whole body exposure for 24 weeks (6 hr/weekday plus 4 hr/Saturday for a total inhalation exposure of about 820 hours) at 1 ppm and 2.5 ppm. Subjects in the 1 ppm group were 4 female cats and 10 juvenile male Wistar rats (initial mean rat weight of 110 g). There was no measurable toxicity at 1 ppm. The 2.5 ppm group had the same numbers of cats and rats, plus 4 female guinea pigs. This dose did not alter liver function (sulfobromophthalein test) and did not alter hematology profile nor the color of the blood. Histopathology of 2.5 ppm animals indicated "fatty liver infiltration" in some cats and swelling of kidney tubular epithelium in some rats. Consulting pathologists had varying opinions as to whether these findings represented treatment effects. Brains of some 2.5 ppm group animals suggested "slight and non-specific changes of the Purkinje cells," judged to be agonal or post-mortem changes. Higher treatment groups received 5.0 ppm PH_3 (eight 6-hr doses for 48 hr, or a combination of 6 hr and 4 hr treatments for a total of 80 hr). Four of 6 cats and nearly all rodents died at 5 ppm, usually before completion of the 48 hr exposure time. Other rats were administered about 200 ppm PH_3 in subsequent tests, either with or without prior exposure to 1 ppm phosphine, for a total of 102 hr: the pre-treatment at 1 ppm had no influence on time of death nor on histopathology of decedents. In summary, this study pre-dates modern guidelines in many respects, and this study is not suitable for establishment of NOEL's. Data are consistent with the concept that "chronic" toxicity of PH_3 is either non-existent, or is limited to exposures close to lethal levels on subacute exposure. This is consistent with FIFRA studies in this Summary. No worksheet. Aldous, 2/24/02.

51882-015 186145 Mansdorf, S. Z., T. W. Knupp, and M. D. Bold, "Phosphine exposure monitoring for applicators, workers, and nearby persons, Volume I," report by S. Z. Mansdorf & Associates, 4/15/88. Study was prepared to evaluate exposures to persons resulting from phosphine gas generated from aluminum or magnesium phosphide. This record will be routed to Worker Health and Safety Branch for review. Aldous, 4/26/02.

51882-014 186142 Shimizu, Y., "Acute inhalation toxicity evaluation of hydrogen phosphide in rats," Nomura Research Institute, May, 1982. Phosphine was generated by addition of water to magnesium phosphide in closed chambers. Chamber phosphine levels were measured by "Kitagawa gas detector tubes of vacuum method and detector tubes manufactured by Dräger-Kag." Based on pilot tests, conditions of the present study were 1-hr exposures to CD rats (10/sex) at phosphine levels of 150, 165, 182, 200, 220, and 242 ppm. Estimated LD_{50}'s were 204 and 179 ppm for M and F, respectively. Common observations included tonic convulsions, sudden running about, and death in a prone position. All deaths occurred between just prior to end of exposure and 7 hr following end of exposure. Food consumption of both sexes was generally diminished on the first day after exposure, then returned to normal on day 2. Body weight was reduced at 220 ppm on day 1, with subsequent weight gain comparable between groups thereafter. Rats were necropsied upon spontaneous death or at day 14, survival permitting. Several tissues were preserved in formalin, however it is not clear whether or not they were evaluated microscopically. Investigators indicated that macroscopic evaluations found no alterations, and made no mention of histopathology. Supplemental data, not applicable to current data requirements. No worksheet. Aldous, 4/26/02.

51882-014 186144 Muthu, M., M. K. Krishnakumari, [no initials given] Muralidhara, and S. K. Majumder, "A study on the acute inhalation toxicity of phosphine to albino rats," Bull. Environ. Contam. Toxicol. 24:404-410 (1980). Investigators evaluated acute effects on CTF-Wistar rats of phosphine generated by addition of water to two aluminum phosphide materials in closed exposure chambers. Many features were not standardized, making the study of little value for hazard evaluation. LC_{50} estimations for phosphine generated from the two compounds were 28 ppm (mean exposure time of 5.2 hr) and 33 ppm (mean exposure time of 7.4 hr). Unacceptable. No DPR worksheet. Aldous, 4/26/02.

51882-014 186143 Morgan, D. L., M. P. Moorman, M. R. Elwell, R. E. Wilson, S. M. Ward, M. B. Thompson, R. W. O'Connor, and H. C. Price, "Inhalation toxicity of phosphine for Fischer 344 rats and B6C3F1 mice," Inhalation Toxicology 7:225-238 (1995). Male rats and mice, at least 5/group for rats and 10/group for mice, were dosed with 0, 1, 5, and 10 ppm phosphine (from a commercial pressurized cylinder), for four consecutive daily exposures at 6 hr/session in a pilot study. Responses were limited to 10 ppm, as follows. All rats died and all mice were in moribund condition by the end of the fourth exposure. At 10 ppm, mice were anemic (reduced RBC counts, Hb, HCT, platelet counts, lymphocyte counts, and monocyte counts). Clinical chemistry findings included remarkable increases in ALT and sorbitol dehydrogenase activities, and sharply elevated BUN. The 10 ppm mice had "minimal to mild degeneration and necrosis of the renal tubular epithelium," and "minimal to mild subcapsular foci of hemorrhage and necrosis in the liver." The primary (2-week) study employed at least 6 rats or mice per sex/time point combination at 0, 1.25, 2.5, and 5 ppm. Male rats and mice were killed after 1, 5, or 10 exposures. Female rats and mice were killed after day 10 only. NOEL = 2.5 ppm (2-week exposure led to significant decrease in lung weights in male rats and mice, significant increase in heart weights in female rats and mice, and very slight increase in BUN in male mice). Supplemental study, valid for parameters evaluated. No adverse effects: only exposures approaching the acutely lethal range appear to elicit toxic responses. Aldous, May 1, 2002.